Specifications

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SPECIFICATIONS

- A specification is defined as a list of tests, reference to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should confirm to be considered acceptable for its intended use.
- Specifications are critical quality standards that a proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications

Can be established and used for :

- The release of the final products
- Quality control of raw materials
- Verification of the validity of the manufacturing process
- Maintenance of consistency
- Proper quality control of intermediate products, if any
- Stability testing

Setting Specifications

- Selection of tests to be included in the specifications is product specific. The rationale used to establish the acceptable range of acceptance criteria should be described.
- Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, and data from stability studies, and relevant development data.

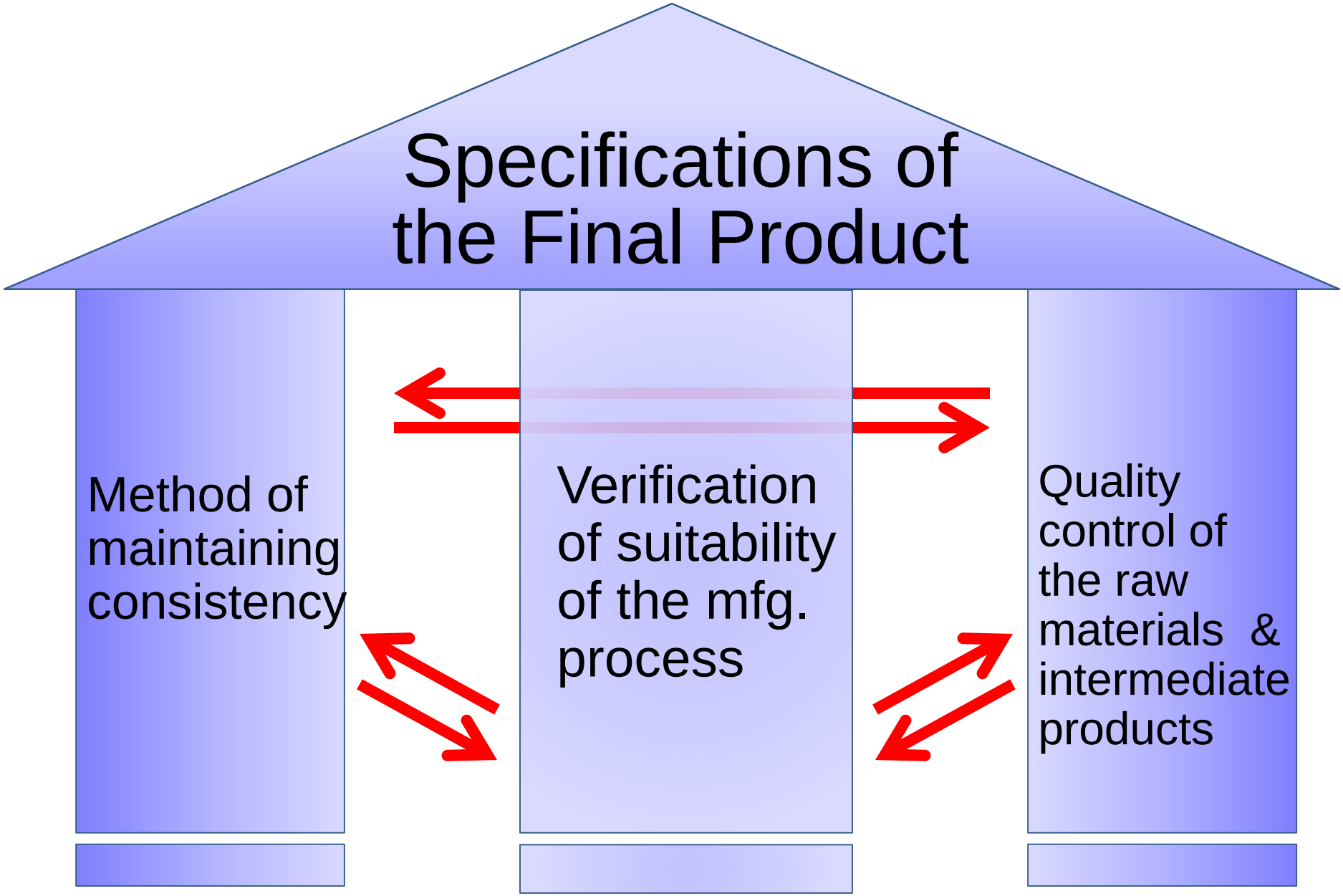
Specification as a typical product element

- To ensure product quality and consistency, a relevant combination of product and process elements is important.
- Specification is a typical product element

Specifications of the Final Product

Specifications of the final product shall be set and justified from the standpoint of achieving the purpose of quality control as a whole, taking into consideration the mutually complementary relationships among

1) Verification of the suitability of the manufacturing process
2) The method of maintaining consistency, and
3) Quality control of the raw materials and intermediate products


Specifications of the Final Product
Method of maintaining consistency
Verification of suitability of the mfg. process
Quality control of the raw materials & intermediate products

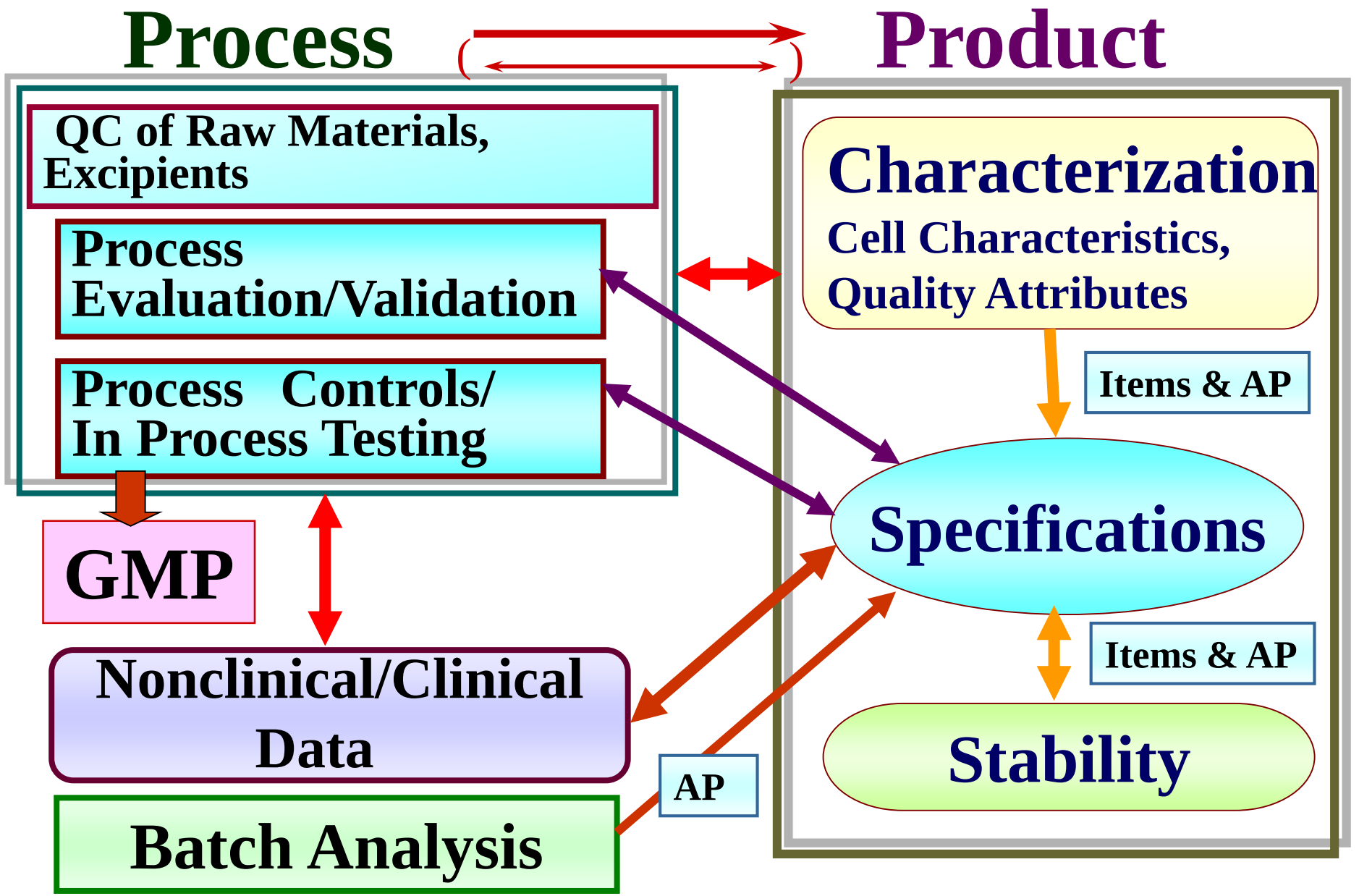
Specifications for MAA

- It should be noted that the quality control strategy including specification should be enriched and developed along with the progress of clinical trials.
- It is desirable that specifications of the final products can be included critical product attributes that may impact the safety and efficacy of the product.
- Including of product attributes for monitoring manufacturing consistency is also very important.

JUSTIFICATION OF THE SPECIFICATION

Since specifications are chosen to confirm the quality rather than to fully characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes.

Elements for Ensuring Product Quality and Consistency



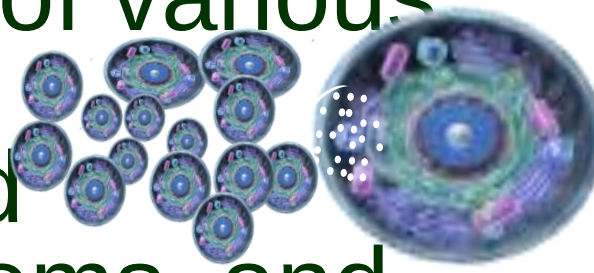
Specific Points to Consider for Specifications of hCTPs

- The general considerations addressed so far can almost be applicable for hCTPs.
- However, setting specification for hCTPs as well as its role in the medical treatment would be different from those of traditional biological and biotechnological protein products described in ICH Q6B.

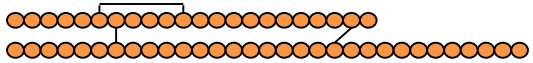
Differences between Cells and Proteins

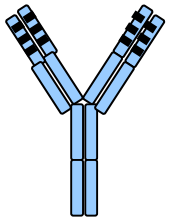
It should be emphasized that the active ingredient of hCTPs

- Is cells that are assembly of various cell subpopulations that are inherently variable and heterogeneous living systems, and



- Have extremely complex biological and structural features in comparison with protein products whose quality attribute can be shown at chemical and molecular levels

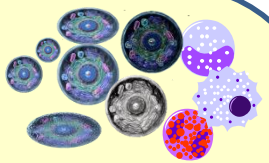




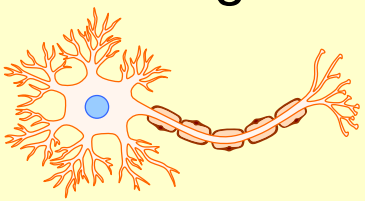
Differences between Cells and Proteins

Also,it is anticipated to develop a wide variety of hCTPs that have individually specific nature and functions.

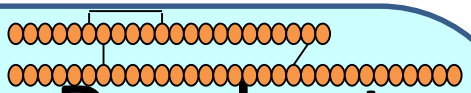
hCTPs



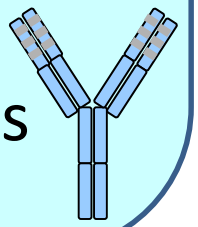
- Cultured Epidermis
- Cartilage
- Corneal Epithelium
- Retinal Pigment Epithelium
- Skeletal Myoblast cell
- Cardiomyocyte
- Dopamine-producing Neurons
- Platelets
- ……



Protein Products



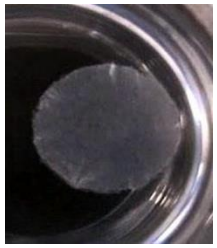
The structural integrity and characterization of the product comes from the results of product specific structural analysis, as well as a wide variety of physicochemical, biological, and immunochemical tests



How to consider specifications on hCTPs?

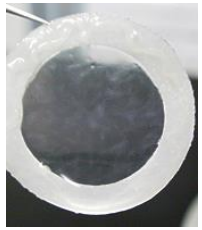
Cultured Epidermis

Cultured Cartilage

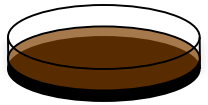


Cardiomyocyte

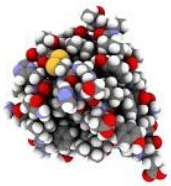
Skeletal Myoblast



Corneal Epithelial



Retinal Pigment Epithelium



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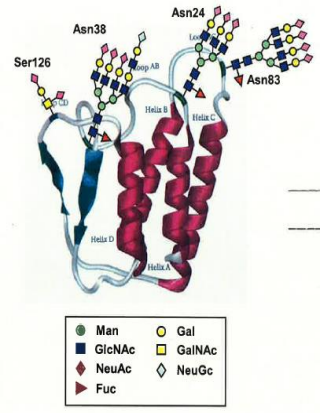
LGHSLGIPWA PLSSCPSQAL QLAGCLSQLH SGLFLYQGLL QALEGISPEL

GPTLDTLQLD VADFATTIWQ QMEELGMAPA LQPTQGAMPA FASAFQRRAG

GVLVASHLQS FLEVSYRVLR HLAQP

G-CSF



rhEPO

- **Amio Acid Sequences**
- **N- and O-Glycan Str.**
- **Physicochemical–**
  Biological–
  Immunological–
  Properties
- **Quality Attributes**

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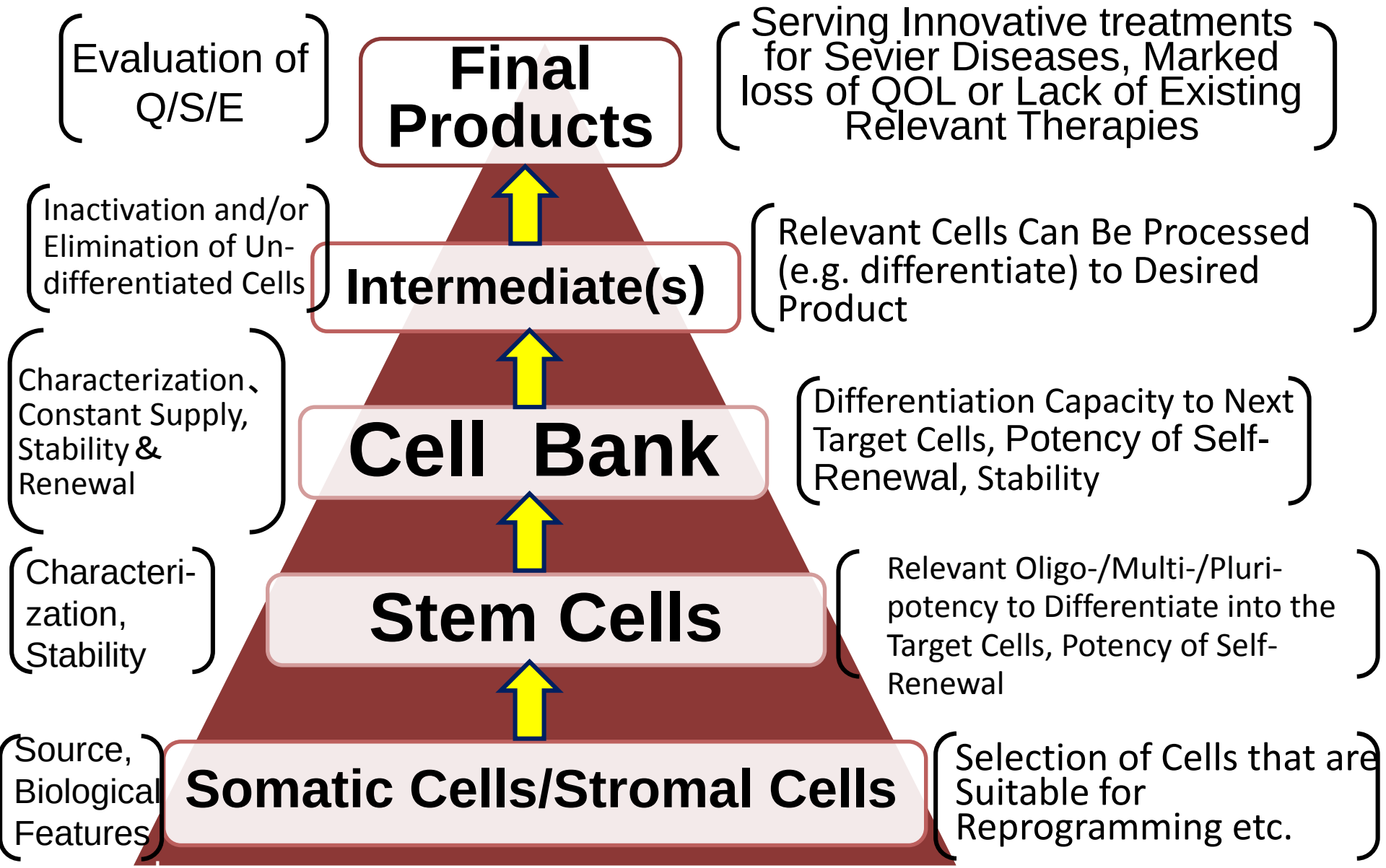
Well characterized by Biochemical Analysts

Specific Features of hCTPs relate to Their Specifications

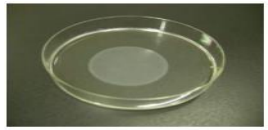
- Cells can be characterized and controlled from starting cells through final products at critical stages.
- This emerges, converges, and then specifies the profile of the final products.
- Therefore, specification of the final product of hCTPs can be set taking into consideration such a series of cell characterizations as a whole.


Evaluation of Q/S/E
Final Products
Serving Innovative treatments for Sevier Diseases, Marked loss of QOL or Lack of Existing Relevant Therapies
Inactivation and/or Elimination of Un-differentiated Cells
Intermediate(s)
Relevant Cells Can Be Processed (e.g. differentiate) to Desired Product
Characterization、Constant Supply, Stability & Renewal
Cell Bank
Differentiation Capacity to Next Target Cells, Potency of Self-Renewal, Stability
Characteri-zation, Stability
Stem Cells
Relevant Oligo-/Multi-/Pluri-potency to Differentiate into the Target Cells, Potency of Self-Renewal
Source, Biological Features
Somatic Cells/Stromal Cells
Selection of Cells that are Suitable for Reprogramming etc.

Specific Features of hCTPs relate to Their Specifications

- Medical specialists engage at critical stages of Cell Therapy using hCTPs (e.g., biopsy, transplantation) .

- In some cases such as skin, cartilage, cornea, and myocardial cell, the medical specialists might be the best assessors of certain quality of hCTPs in a special field rather than biochemical analysts.



- Such specific Medical Translation can be taken into considerations when setting specification of the final product of hCTPs.

Specifications for the final product (1)

Specifications will differ among final products, depending upon:

- type and properties of the desired cells and tissues
- mfg methods
- intended clinical use
- mode of administration of each product
- stability, and
- test methods available

These differences shall be taken into consideration when setting the acceptance criteria and test procedures.

Specifications for the final product (2)

There may be general considerations applicable in individual cases, while there also may be specific requirement in an individual case.

Specifications for the final product (3)

When setting specifications for an individual final product, it may be necessary to refer to the quality control parameters and tests shown below.
It should be noted that they are just examples, and it is necessary to provide the rationale for these specifications.

- The Cell number and cell viability
- Tests of Identity
- Tests of Purity
- Tests for cell-derived undesirable physiologically active substances
- Tests for process-related impurities
- Sterility tests and tests for mycoplasma
- Endotoxin tests
- Virus tests
- Efficacy tests
- Potency tests
- Mechanical compatibility tests

Cell number and cell viability

The number and viability of cells that are active ingredients in the final product, or in an appropriate intermediate product, if required, should be determined.

At the beginning of the clinical trial, it is acceptable to set provisional acceptance criteria based on actual measured values obtained for a small number of test samples.

Tests of identity

Confirm that the cells are the intended target cells using markers for critical cell characteristic(s)

- biochemical markers
- morphological characteristics
- immunological markers
- characteristic products, and
- other appropriate genotypes or phenotypes of the intended target cells and tissues

Test of purity

To test the purity of the cell population in a final product, set the test parameters, test methods, and acceptance criteria for evaluating and controlling nontarget cells

- undifferentiated cells
- cells exhibiting abnormal growth
- transformed cells
- presence of any other contaminating cells

At the beginning of the clinical trial, it is acceptable to set provisional acceptance criteria based on actual measured values obtained for a small number of test samples.

Tests for cell-derived undesirable physiologically active substances

Specify the appropriate tests for determining the permissible dose limits of any potential undesirable physiologically active substances that are derived from the target cells, if the presence of such substances in the product is presumed to clearly impact the safety of the patients.

At the beginning of the clinical trial, it is acceptable to set provisional acceptance criteria based on actual measured values obtained for a small number of test samples.

Tests for process-related impurities

For substances that may be present in the final product, for instance, as contaminants, residues, as newly generated products or degradation products that may have deleterious effect on the quality and safety:

1) prove that the substance is not present in the final product using the results of process evaluation for the elimination of the substance or the results of in-process control of the substance or
2) establish appropriate tests to control the amount of the substance in the final product within permissible levels.

At the beginning clinical trial, it is acceptable to set provisional acceptance .

Sterility tests and tests for the absence of mycoplasma

The sterility of the final product should be demonstrated in tests before use in a patient. Appropriate tests confirming the absence of mycoplasma should also be carried out.

- If the results of the sterility and other tests of the final product can be obtained only after administration to the patient, the proper measures for dealing with the potential lack of sterility should be established beforehand.
- In such cases, the intermediate products must be demonstrated to be sterile, and sterility should be strictly maintained in all processes leading up to the final product.

Sterility tests and tests for the absence of mycoplasma

- If a product from the same facility and same process has already been used in patients, its sterility must be confirmed by testing it in all patients.
- When tests must be conducted for each clinical application and if the results of sterility and other tests can be obtained only after administration to the patient, the decision on whether the clinical application should proceed will be determined based on the most recent data.
- However, even in this case, sterility tests and other tests shall be performed on the final product.

Endotoxin tests

Perform an endotoxin test, considering the impact of a potential contaminant in the samples. The acceptance criteria do not necessarily depend on the actual measured values. It is recommended to set acceptance criteria considering the safety ranges given in Pharmacopoeias and/or any other relevant compendia based on a single dose of the final product. Endotoxin testing can be established as an in-process control test; however, in such cases, specify criteria, including validation results, and provide the justification.

Virus tests (Autologous hCTPs)

- If the absence of HBV, HCV, HIV, and HTLV cannot be proven at the patient level, and if these viruses may proliferate in the cells, conduct virus titer tests and confirm that administration of the final products will not lead to any adverse effects on the patient. This does not apply if tests proving the absence of viruses are performed on intermediate products or at the cell bank.
- If components of biological origin are used in the mfg. process, it may be necessary to conduct tests on the final product for viruses originating from those components. However, whenever possible, it is preferable to verify the absence of contamination by testing or via process evaluation at the upstream stage, including tests on the original components.

Virus tests (Allogeneic hCTPs)

- To test when using cells that are not banked in either raw materials or mfg. processes and are from donors not cleared of infection in the window period, and in the cells HBV, HCV, HIV, or HTLV can propagate.
- If components of biological origin are used in the mfg. process, it may be necessary to consider performing tests on the final product for viruses originating from those components. However, whenever possible, it is preferable to determine that there is no contamination via testing or process evaluation at the upstream stage, including the original component.

Specific Biological Activity Testing

In some instances, it will be necessary to consider a specific biological activity testing (a qualitative biological assay) that takes into consideration the cell type, intended clinical use, or distinctive characteristics of the cells.

At the beginning of the clinical trial, it is acceptable to set provisional acceptance criteria based on measured values obtained for a small number of test samples.

Potency assay

If the secretion of a specific physiologically active substance from the cells or tissues is responsible for the efficacy or the essential effect of a product during its intended clinical use, establish test parameters and/or acceptance criteria related to this substance in order to demonstrate the intended effect.
Set acceptance criteria for potency or the amount of the active substance in question produced by the desired cells or for an expression product secreted from the cells when a transgene was introduced.

At the beginning of the clinical trial, it is acceptable to set provisional acceptance criteria based on measured values obtained for a small number of test samples.

Mechanical compatibility tests

For products that require a certain degree of mechanical strength, set acceptance criteria to confirm mechanical compatibility and durability that take into account the site of application.

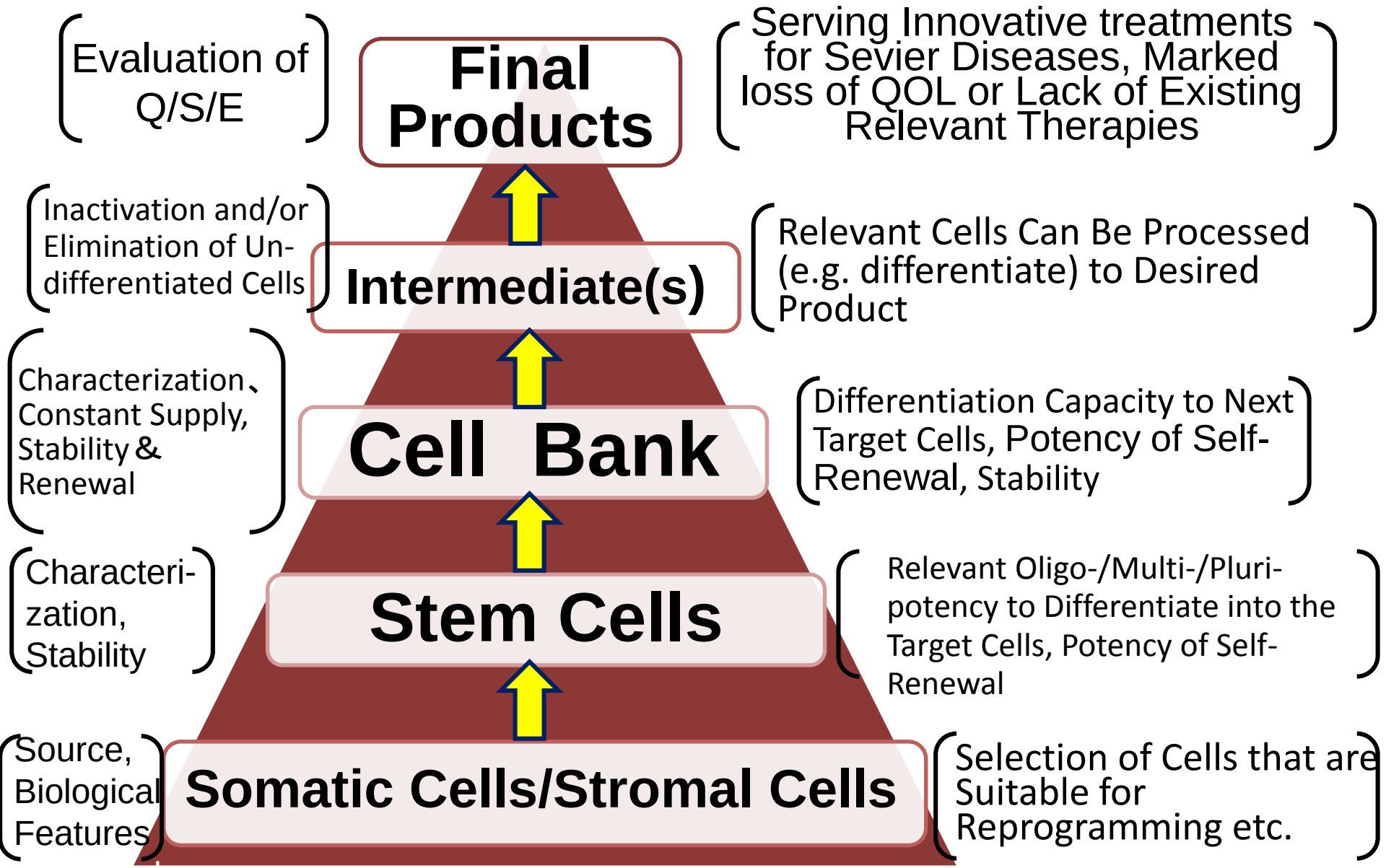
At the beginning of the clinical trial, it is acceptable to set provisional acceptance criteria based on actual measured values obtained for a small number of test samples.

Provisional Summary

- Know Product in Question
- Keep Process Robustness
- Test on Viability, Identity, Purity, Sterility…
- Take Relevant Balance to Medical Needs
- Regard as an Element of Medical Translation
- Rely on Institution and Doctor
- Refine Spec. at Post Approval Stage
- Accumulate Expertise
- Develop Relevant Analytical Methodology
- Make Decision by Scientific Common Sense

Keep Process Robustness

Specifications for hCTPs are more linked to a manufacturing process in terms of a series of cell characterizations. Cells can be characterized and controlled from starting cells through final products at critical stages. In this sense we need to keep process robustness as a specific feature of hCTPs in relation to specifications.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Characteri-zation, Stability
Stem Cells
Relevant Oligo-/Multi-/Pluri-potency to Differentiate into the Target Cells, Potency of Self-Renewal
Source, Biological Features
Somatic Cells/Stromal Cells
Selection of Cells that are Suitable for Reprogramming etc.

Regard as an Element of Medical Translation
Rely on Institution and Doctor

Specifications for hCTPs are well linked to clinical procedures as an element of medical translation. Medical specialists engage at critical stages of Cell Therapy using hCTPs (e.g., biopsy, transplantation) , relying on institution and doctors.

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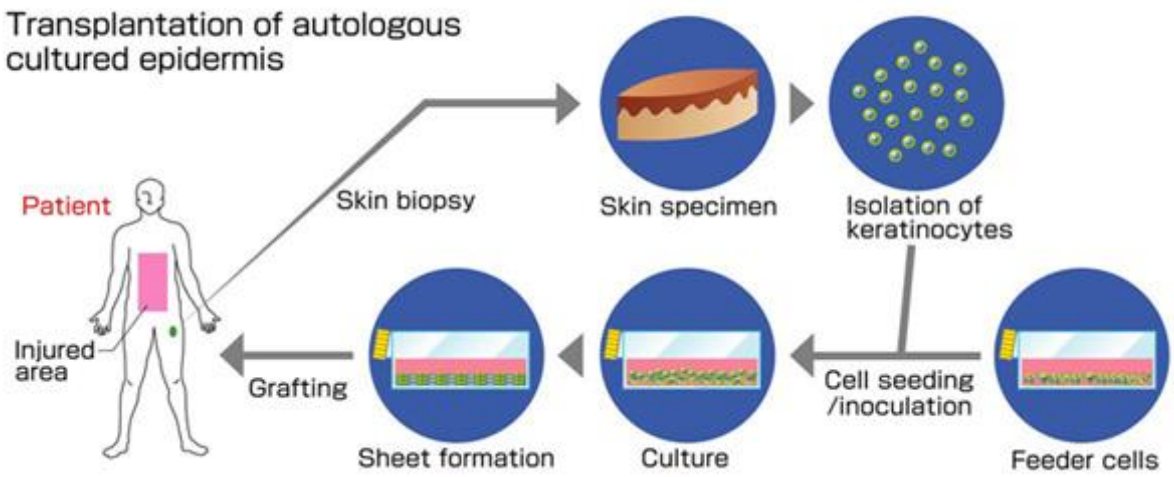
Human Cell Therapy Products (hCTPs)



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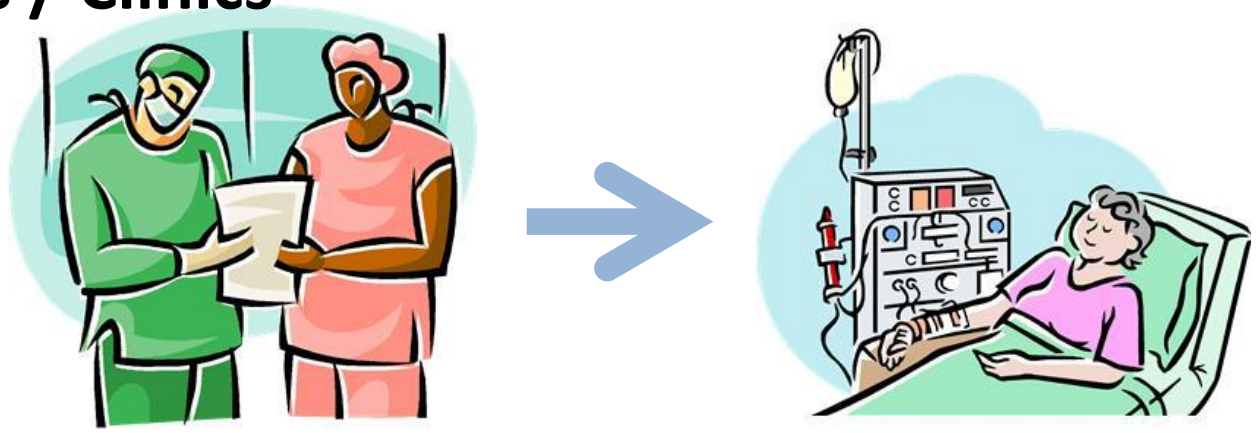
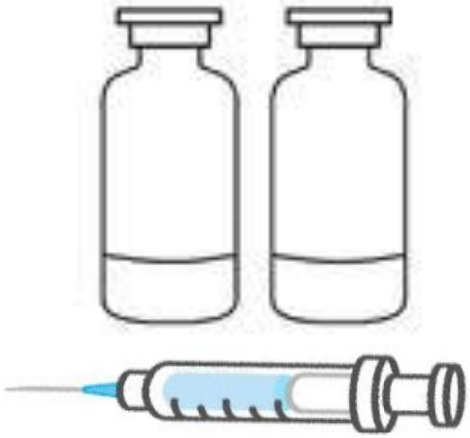
Hospitals / Clinics



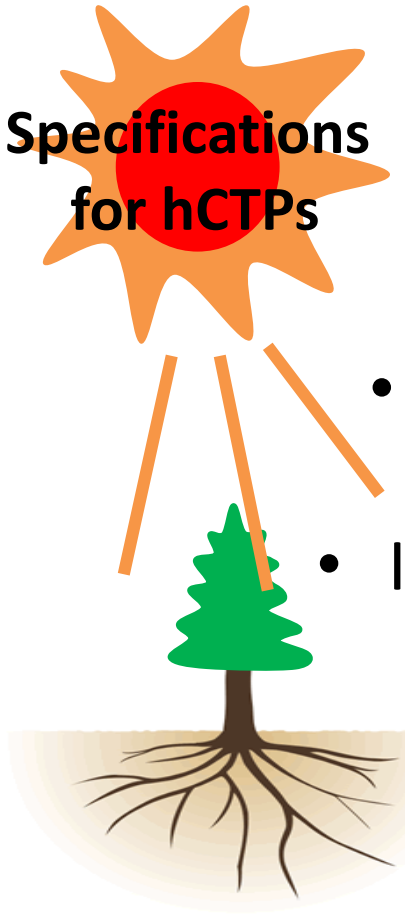
Assessors of the quality of hCTPs

Biologics



hCTPs

Fertilizer and Mulch



- Research in Academia
- Innovative Manufacturer and Distributor
- Regulation with Sound Science

Thank you for your attention!